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Evaluation of Dual Versus Triple Therapy by Landmark Analysis in the RE-DUAL PCI Trial

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ABSTRACT

OBJECTIVES The aim of this study was to explore the early versus late benefits and risks of dabigatran dual therapy versus warfarin triple therapy in the RE-DUAL PCI (Randomized Evaluation of Dual Antithrombotic Therapy With Dabigatran Versus Triple Therapy With Warfarin in Patients With Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) trial.

BACKGROUND Patients with atrial fibrillation who undergo percutaneous coronary intervention are at increased risk for both bleeding and thrombotic events.

METHODS A total of 2,725 patients with atrial fibrillation underwent percutaneous coronary intervention and were randomized to receive dabigatran 110 mg, or dabigatran 150 mg plus a $P2Y_{12}$ inhibitor (and no aspirin), or warfarin plus a $P2Y_{12}$ inhibitor plus aspirin. Landmark analysis was performed at 30 and 90 days.

RESULTS There was a consistent and large reduction in major or clinically relevant nonmajor bleeding in patients randomized to dual therapy during the first 30 days (110 mg: hazard ratio [HR]: 0.45; 95% confidence interval [CI]: 0.31 to 0.66; $p < 0.0001$; 150 mg: HR: 0.46; 95% CI: 0.30 to 0.72; $p = 0.0006$) compared with warfarin triple therapy. There was early net clinical benefit in both dabigatran groups versus warfarin (110 mg: HR: 0.65; 95% CI: 0.47 to 0.88; $p = 0.0062$; 150 mg: HR: 0.54; 95% CI: 0.37 to 0.79; $p = 0.0015$), due to larger reductions in bleeding than increased thrombotic events for dabigatran 110 mg and bleeding reduction without increased thrombotic risk for dabigatran 150 mg dual therapy versus warfarin triple therapy. After the removal of aspirin in the warfarin group, bleeding remained lower with dabigatran 110 mg and was similar with dabigatran 150 mg versus warfarin.

CONCLUSIONS In RE-DUAL PCI, in which patients in the dual-therapy arms were treated with aspirin for an average of only 1.6 days, there was early net clinical benefit with both doses of dabigatran dual therapy, without an increase in thrombotic events with dabigatran 150 mg. This could be helpful in the subset of patients with elevated risk for both bleeding and thrombotic events. (J Am Coll Cardiol Intv 2021;14:768–80) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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Atrial fibrillation is a disease of increasing importance in the aging population, affecting approximately 33 million patients worldwide (1). An increasing number of patients with atrial fibrillation who undergo percutaneous coronary intervention (PCI) require antiplatelet therapy in addition to systemic anticoagulation, which for many years consisted of warfarin plus low-dose aspirin plus a $P2Y_{12}$ inhibitor (2–9). In recent years, however, randomized clinical trials have shown improved bleeding and similar efficacy with different antithrombotic strategies (10–14). Subsequently, it was suggested that triple-antithrombotic therapy may be unnecessary and even harmful for many patients in an era of newer generation stents and direct oral anticoagulants (DOACs) (15–20).

A recent meta-analysis, which included WOEST (What Is the Optimal Antiplatelet & Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting), RE-DUAL PCI (Randomized Evaluation of Dual Antithrombotic Therapy With Dabigatran Versus Triple Therapy With Warfarin in Patients With Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention), PIONEER AF (A Study Exploring Two Strategies of Rivaroxaban [JNJ39039039; BAY-59-7939] and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention), and AUGUSTUS (A Study of Apixaban in Patients With Atrial Fibrillation, Not Caused by a Heart Valve Problem, Who Are at Risk for Thrombosis [Blood Clots] Due to Having Had a Recent Coronary Event, Such as a Heart Attack or a Procedure to Open the Vessels of the Heart), showed that patients who received a DOAC plus a $P2Y_{12}$ inhibitor after PCI had less bleeding than those who received a vitamin K antagonist agent plus dual-antiplatelet therapy (21). However, it has also recently been suggested that a higher risk for stent thrombosis may exist when withdrawing aspirin, especially in the first month after PCI (22).

The RE-DUAL PCI trial compared 110- and 150-mg doses of dabigatran plus clopidogrel or ticagrelor versus triple therapy (23). It was found that patients receiving dabigatran dual therapy versus warfarin triple therapy had a significantly reduced bleeding risk; dabigatran dual therapy was noninferior to warfarin triple therapy with respect to death or thromboembolic event (DTE) or unplanned revascularization (24). We have conducted a landmark analysis of the RE-DUAL PCI trial to understand whether dabigatran, aspirin cessation, or both contributed to the lower bleeding rates in the dual-therapy arms versus warfarin. We also focused on the early time period when aspirin was withdrawn in the 2 dabigatran groups to explore thrombotic events between the 2 different dosing strategies of dabigatran dual therapy.

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ABBREVIATIONS AND ACRONYMS

BMS = bare-metal stent(s)

CI = confidence interval

CRNM = clinically relevant nonmajor

DES = drug-eluting stent(s)

DOAC = direct oral anticoagulant

DTE = death or thromboembolic event

HR = hazard ratio

ISTH = International Society on Thrombosis and Hemostasis

PCI = percutaneous coronary intervention

METHODS

STUDY POPULATION AND TRIAL DESIGN. This analysis included patients enrolled in the RE-DUAL PCI trial, an open-label multicenter, randomized clinical trial, which enrolled patients with nonvalvular atrial fibrillation who had undergone PCI. Detailed methods and outcomes of this trial have been published previously (23,24). At the time of randomization, all patients in the United States and younger patients in other countries (<80 years of age; <70 years of age in Japan) were assigned to receive warfarin triple therapy (warfarin plus clopidogrel or ticagrelor plus aspirin), dual-antithrombotic therapy with dabigatran 110 mg twice daily plus clopidogrel or ticagrelor, or dual-antithrombotic therapy with dabigatran 150 mg twice daily plus clopidogrel or ticagrelor in a 1:1:1 ratio. Older patients outside the United States (≥80 years of age; ≥70 years of age in Japan) were randomized to either warfarin triple therapy or dabigatran 110 mg twice daily plus clopidogrel or ticagrelor in a 1:1 ratio. In the triple-therapy group, aspirin was discontinued after 90 days in patients with drug-eluting stents (DES) and 30 days in patients with bare-metal stents (BMS). Subsequently, all patients were treated with dual-antithrombotic therapy with a $P2Y_{12}$ inhibitor plus warfarin or their respective doses of dabigatran for 12 months. Because of the differential timing of aspirin cessation among BMS patients, they were not included in the exploratory landmark analysis at 90 days (but are included in the Supplemental Appendix). However, they were included in the primary 30-day landmark analysis and the net clinical benefit analysis. Institutional Review

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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TABLE 1 Analysis of Time to First Adjudicated ISTH MBE or CRNMBE, DTE or Unplanned Revascularization, or NCB Event: ISTH MBE/CRNMBE or DTE or Unplanned Revascularization

	Dabigatran 110 mg DAT	Warfarin Triple*	HR (95% CI)	p Value	Dabigatran 150 mg DAT	Warfarin Triple†	HR (95% CI)	p Value
Before 30 days								
Total patients	981	981			763	764		
ISTH MBEs/CRNMBEs	40 (4.1)	86 (8.8)	0.45 (0.31–0.66)	<0.0001	29 (3.8)	61 (8.0)	0.46 (0.30–0.72)	0.0006
DTE or unplanned revascularization	28 (2.9)	20 (2.0)	1.39 (0.79–2.47)	0.26	12 (1.6)	17 (2.2)	0.70 (0.33–1.46)	0.34
NCB	66 (6.7)	100 (10.2)	0.65 (0.47–0.88)	0.0062	41 (5.4)	74 (9.7)	0.54 (0.37–0.79)	0.0015
After 30 days								
Total patients	912	867			721	679		
ISTH MBEs/CRNMBEs	111 (11.9)	178 (20.3)	0.55 (0.43–0.69)	<0.0001	125 (17.1)	135 (19.6)	0.82 (0.65–1.05)	0.12
DTE or unplanned revascularization	121 (12.7)	111 (11.7)	1.09 (0.84–1.40)	0.53	78 (10.4)	81 (11.0)	0.94 (0.69–1.28)	0.67
NCB	196 (21.5)	249 (28.7)	0.70 (0.58–0.85)	0.0002	181 (25.1)	185 (27.2)	0.88 (0.72–1.08)	0.22

Values are n (%). All patients treated with bare-metal stents or drug-eluting stents, randomized to receive warfarin triple therapy for 30 or 90 days and then warfarin plus a $P2Y_{12}$ inhibitor without aspirin versus dabigatran 110 mg or 150 mg plus a $P2Y_{12}$ inhibitor. For the dabigatran 110 mg versus warfarin comparison, the model was stratified by age, nonelderly versus elderly (<70 or ≥70 years in Japan and <80 or ≥80 years elsewhere). For the dabigatran 150 mg versus warfarin comparison, an unstratified model was used, as with other analyses. *All patients who received warfarin triple therapy. †All patients who received warfarin triple therapy and who qualified for 150-mg dabigatran dual therapy.

CI = confidence interval; CRNMBE = clinically relevant nonmajor bleeding event; DAT = dual-antithrombotic therapy; DTE = death or thromboembolic event; HR = hazard ratio; ISTH = International Society on Thrombosis and Hemostasis; MBE = major bleeding event(s); NCB = net clinical benefit.

Board approval was obtained at all sites, and all patients provided written informed consent.

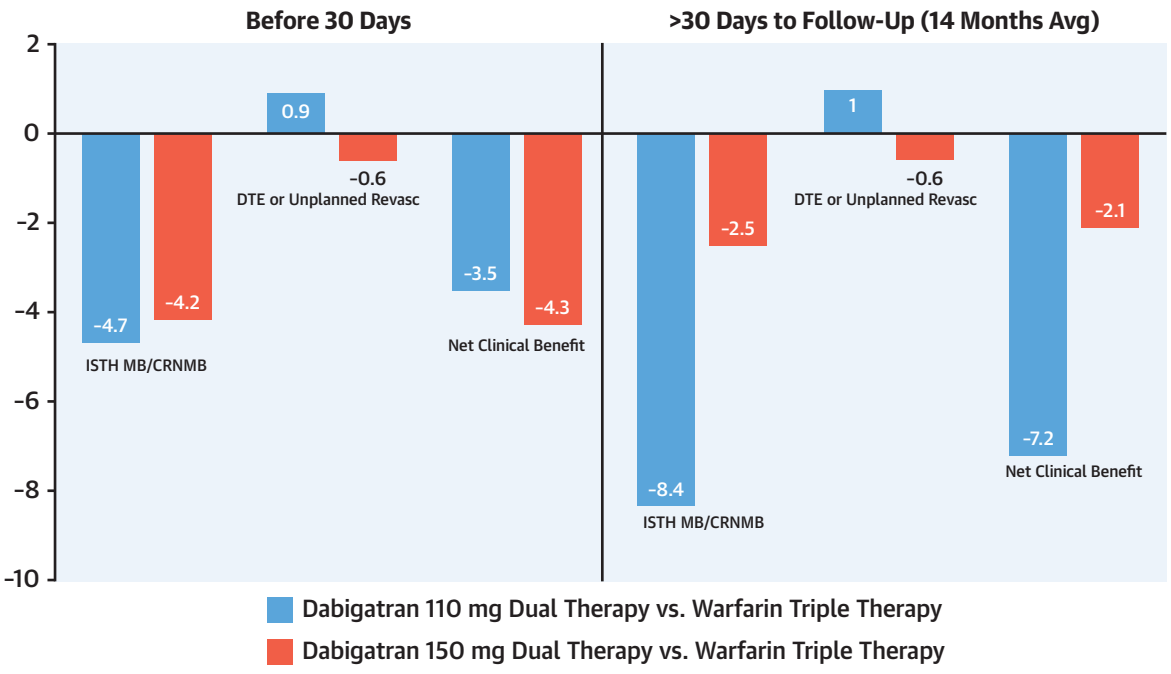
ENDPOINTS AND FOLLOW-UP. The primary endpoint was time to the first major or clinically relevant nonmajor (CRNM) bleeding event, as defined by the International Society on Thrombosis and Hemostasis (ISTH). The main efficacy endpoint was a composite of time to DTE (myocardial infarction, stroke, or systemic embolism) or unplanned revascularization. Other secondary endpoints were time to DTE, stent thrombosis, or myocardial infarction. All clinical endpoints were centrally adjudicated by independent committee members who were blinded to treatment assignment.

STATISTICAL ANALYSIS. Overall, there were 2,725 patients in the RE-DUAL PCI study, 2,251 of whom (82.6%) had undergone stenting with DES. Time-to-event analyses were performed using Cox proportional hazards regression models. For comparisons involving 110-mg dabigatran dual therapy versus warfarin triple therapy, the models were stratified by age (older [≥70 years in Japan and ≥80 years elsewhere], non-older [<70 years in Japan and <80 years elsewhere]), as had been done in the primary trial. Comparisons involving 150-mg dabigatran dual therapy versus warfarin triple therapy are not stratified for age, because older patients outside the United States were excluded. As in the original trial, comparisons with the 150-mg dabigatran dual-therapy group were made with patients who received warfarin triple therapy who were also eligible to receive 150-mg dabigatran dual therapy. With growing interest in events in the first 30 days, we performed a landmark analysis at 30 days for all patients (DES and BMS) (22). For this we also performed a net clinical benefit analysis; the net clinical benefit endpoint was time to first ISTH major bleeding or CRNM bleeding or DTE or unplanned revascularization event among all patients who received DES or BMS (25) (see the Supplemental Appendix for a schema of methods). Baseline characteristics and event rates are summarized as number (percentage). Event rates were compared using Cox proportional hazards regression models, with corresponding Wald confidence limits for the hazard ratio (HR).

Landmark analysis was secondarily conducted on the basis of the pre-specified timing for cessation of aspirin in the warfarin triple-therapy groups at 90 days for DES and 30 days for BMS (see Supplemental Figure 1) (26–32). Surviving patients who were free from the primary bleeding endpoint at the landmark cutoffs were included for landmark analysis of the primary endpoint. Surviving patients were also included for landmark analysis of the primary and secondary efficacy endpoints, as well as net clinical benefit, if they were free from the respective event at the landmark cutoffs. Composite and individual endpoints were compared using the aforementioned landmarks.

Recurrent events analysis was conducted using the Prentice, Williams, and Peterson gap time model. Piecewise constant regression models were also used in a time-dependent fashion, dividing the time period into 2 intervals before and after cutoff and considering that hazards are proportional within time

CENTRAL ILLUSTRATION **30-Day Landmark: Absolute Risk Difference (%) in Patients Treated With Dabigatran Dual Therapy and Warfarin Triple Therapy**



Peterson, B.E. et al. J Am Coll Cardiol Intv. 2021;14(7):768–80.

Absolute risk difference during the first 30 days among patients who received dabigatran 110 mg plus a $P2Y_{12}$ inhibitor versus warfarin triple therapy and dabigatran 150 mg plus a $P2Y_{12}$ inhibitor versus warfarin triple therapy. Net clinical benefit was a composite of International Society on Thrombosis and Hemostasis (ISTH) major bleeding or clinically relevant nonmajor bleeding and death or thromboembolic event and unplanned revascularization. CRNM = clinically relevant nonmajor bleeding; DTE = death or thrombotic event; MB = major bleeding; Revasc = revascularization.

intervals but not between them. All p values should be regarded as exploratory. Statistical analysis was conducted using SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

STUDY POPULATION AND FOLLOW-UP. There were 2,725 patients enrolled in RE-DUAL PCI, all of whom were included in the main 30-day landmark analysis; 2,251 (82.6%) received a DES and were included in the secondary 90-day analysis. A total of 1,425 patients received dabigatran dual therapy (804 received dabigatran 110 mg and 621 received dabigatran 150 mg), and 826 received warfarin triple therapy. At the beginning of the landmark period, 1,966 patients (84.0%) had not yet experienced ISTH major bleeding or CRNM bleeding (Supplemental Tables 1 and 2, Supplemental Figure 1). For the 2,251 patients who received DES, the mean time from PCI to randomization was 1.5 ± 1.17 days (median 1 day) and median follow-up duration was 12.9 months (interquartile range: 9 to 18 months). A separate analysis was performed on the 404 patients who received BMS.

LANDMARK ANALYSIS AT 30 DAYS AND NET CLINICAL BENEFIT. There were considerable reductions in the primary bleeding endpoint in both doses of dabigatran versus warfarin (110 mg: HR: 0.45; 95% confidence interval [CI]: 0.31 to 0.66; $p < 0.0001$; 150 mg: HR: 0.46; 95% CI: 0.30 to 0.72; $p = 0.0006$). Both doses of dabigatran also had significantly lower rates of recurrent bleeding events, applying the Prentice, Williams, and Peterson gap time model for the whole study period (110 mg: HR: 0.61; 95% CI: 0.51 to 0.72; $p < 0.0001$; 150 mg: HR: 0.77; 95% CI: 0.64 to 0.93; $p = 0.0056$). In the dabigatran 110 mg group, the number of DTE or unplanned revascularization events was numerically higher in the first 30 days (28 [2.9%] vs. (20 [2.0%]; HR: 1.39; 95% CI: 0.79 to 2.47; $p = 0.26$), whereas in the dabigatran 150 mg group, no difference in early risk for thrombotic events

TABLE 2 Secondary Endpoints: Landmark Analysis of Efficacy Endpoints Among All Patients Before and After 30 Days After Randomization

	Dabigatran 110 mg DAT (n = 981)	Warfarin Triple* (n = 981)	HR (95% CI)	p Value	Dabigatran 150 mg DAT (n = 763)	Warfarin Triple† (n = 764)	HR (95% CI)	p Value
First 30 days after randomization								
DTE or unplanned revascularization	28 (2.9)	20 (2.0)	1.39 (0.79–2.47)	0.26	12 (1.6)	17 (2.2)	0.70 (0.33–1.46)	0.34
DTE events	23 (2.3)	16 (1.6)	1.43 (0.75–2.70)	0.27	10 (1.3)	13 (1.7)	0.76 (0.33–1.73)	0.51
Myocardial infarction	13 (1.3)	7 (0.7)	1.84 (0.73–4.62)	0.19	7 (0.9)	6 (0.8)	1.15 (0.39–3.43)	0.80
Stent thrombosis	8 (0.8)	3 (0.3)	‡		6 (0.8)	3 (0.4)	‡	
30 days after randomization								
DTE or unplanned revascularization	121 (12.7)	111 (11.7)	1.09 (0.84–1.40)	0.53	78 (10.4)	81 (11.0)	0.94 (0.69–1.28)	0.67
DTE events	85 (8.9)	67 (7.1)	1.27 (0.92–1.75)	0.14	50 (6.6)	47 (6.4)	1.03 (0.69–1.53)	0.89
Myocardial infarction	31 (3.2)	22 (2.3)	1.40 (0.81–2.42)	0.23	19 (2.5)	16 (2.2)	1.16 (0.60–2.25)	0.66
Stent thrombosis	7 (0.7)	5 (0.5)	1.40 (0.44–4.40)	0.57	1 (0.1)	4 (0.5)	‡	

Values are n (%). The main efficacy endpoint is a combination of DTE events (myocardial infarction, stroke, or systemic embolism) or unplanned revascularization. *All patients who received warfarin triple therapy. †All patients who received warfarin triple therapy and who qualified for 150-mg dabigatran dual therapy. ‡Fewer than 5 events per treatment comparison or not estimable.

Abbreviations as in Table 1.

compared with warfarin could be detected (12 [1.6%] vs. 17 [2.2%]; HR: 0.70; 95% CI: 0.33 to 1.46; p = 0.34) (Table 1).

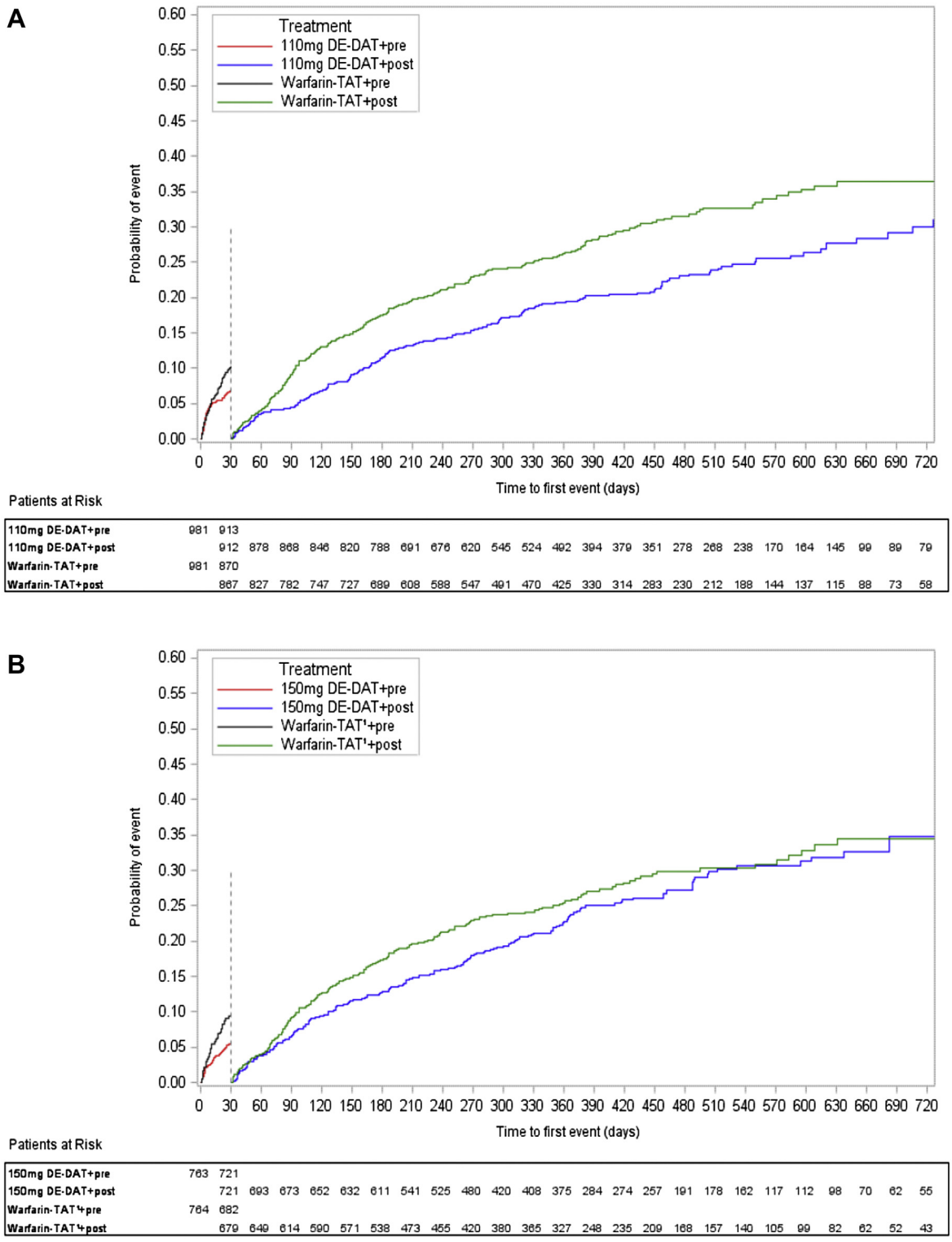
There was early net clinical benefit with both doses of dabigatran dual therapy versus warfarin triply therapy (dabigatran 110 mg vs. warfarin: HR: 0.65; 95% CI: 0.47 to 0.88; p = 0.0062; dabigatran 150 mg vs. warfarin: HR: 0.54; 95% CI: 0.37 to 0.79; p = 0.0015). With dabigatran 110 mg versus warfarin, this was due to larger reductions in bleeding than any increase in thrombotic events. With dabigatran 150 mg versus warfarin, this was due to bleeding reduction without a numeric increase in thrombotic risk (Central Illustration, Table 2). In the Kaplan-Meier analysis of net clinical benefit, visual curve separation between dabigatran 150 mg and warfarin occurred early, at approximately day 5. Although there was also net clinical benefit with dabigatran 110 mg versus warfarin, visual curve separation occurred later, at about 12 days (Figure 1).

After 30 days, patients treated with dabigatran 110 mg dual therapy versus warfarin triple therapy continued to have greater net clinical benefit (HR: 0.70; 95% CI: 0.58 to 0.85; p = 0.0002), whereas patients treated with dabigatran 150 mg versus warfarin had similar net clinical benefit (HR: 0.88; 95% CI: 0.72 to 1.08; p = 0.22). There was a lower risk for bleeding among patients treated with 110-mg dabigatran dual therapy versus warfarin dual therapy and similar risk for bleeding among patients treated with 150 mg versus warfarin. DTE or unplanned revascularization was similar among all groups after 30 days (Table 1, Central Illustration). As expected, HRs from piecewise constant Cox regression models were very similar to those seen in the landmark analyses (Supplemental Table 3).

LANDMARK ANALYSIS AT 90 DAYS AMONG PATIENTS WHO RECEIVED DES. During the first 90 days, there was a reduction in the primary endpoint of ISTH major bleeding or CRNM bleeding in patients who received DES and dabigatran 110 mg dual therapy compared with warfarin triple therapy (6.8% vs. 16.3%; HR: 0.40; 95% CI: 0.29 to 0.54; p < 0.0001) and also in patients who received dabigatran 150 mg dual therapy compared with warfarin triple therapy (9.0% vs. 15.7%; HR: 0.54; 95% CI: 0.39 to 0.75; p = 0.0003) (Figure 2). In the Kaplan-Meier analysis, the curves for ISTH major bleeding or CRNM bleeding begin to separate on approximately day 5 after randomization (Figure 3).

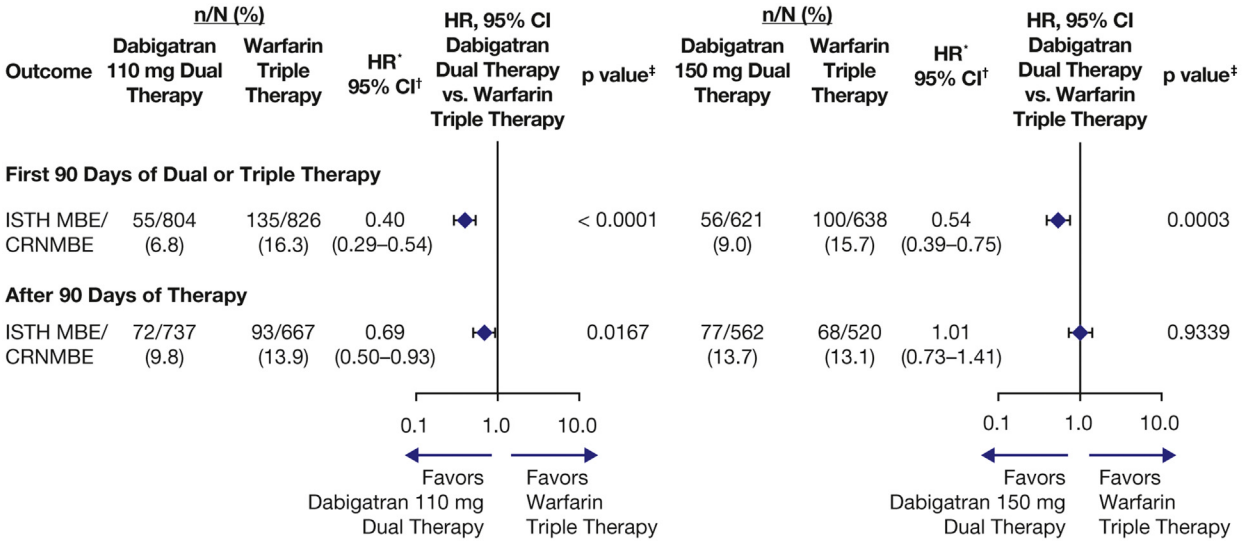
There were similar rates of the secondary efficacy endpoints prior to 90 days in patients treated with dabigatran 110 mg versus warfarin (DTE or unplanned revascularization: 37 [4.6%] vs. 30 [3.6%]; HR: 1.26; 95% CI: 0.78 to 2.04; p = 0.34; stent thrombosis: 7 [0.9%] vs. 4 [0.5%]; HR: 1.78; 95% CI: 0.52 to 6.08; p = 0.36) and in patients treated with dabigatran 150 mg versus warfarin (DTE or unplanned revascularization: 24 [3.9%] vs. 25 [3.9%]; HR: 0.97; 95% CI:

FIGURE 1 **Landmark Analysis of Net Clinical Benefit Endpoint**



All patients treated with drug-eluting stents or bare-metal stents. **(A)** Events before and after the first 30 days after randomization in patients who received 110 dabigatran dual therapy versus warfarin triple therapy. **(B)** Events before and after the first 30 days after randomization in patients who received 150 dabigatran dual therapy versus warfarin triple therapy. DAT = dual-antithrombotic therapy; DE = dabigatran; TAT = triple-antithrombotic therapy.

FIGURE 2 Landmark Analysis of Events Among Patients Who Received Drug-Eluting Stents



[1]Cox proportional hazard model. For the dabigatran 110 mg dual therapy versus warfarin comparison, the model is stratified by age, nonelderly versus elderly [<70 or ≥70 in Japan and <80 or ≥80 years old elsewhere]. For the dabigatran 150 mg dual therapy versus warfarin comparison, an unstratified model is used.

[2]Wald confidence limits.

[3]Wald 2-sided p value from (stratified) Cox proportional hazard model.

[4]For the comparison with dabigatran 150 mg dual therapy, elderly patients outside United States are excluded.

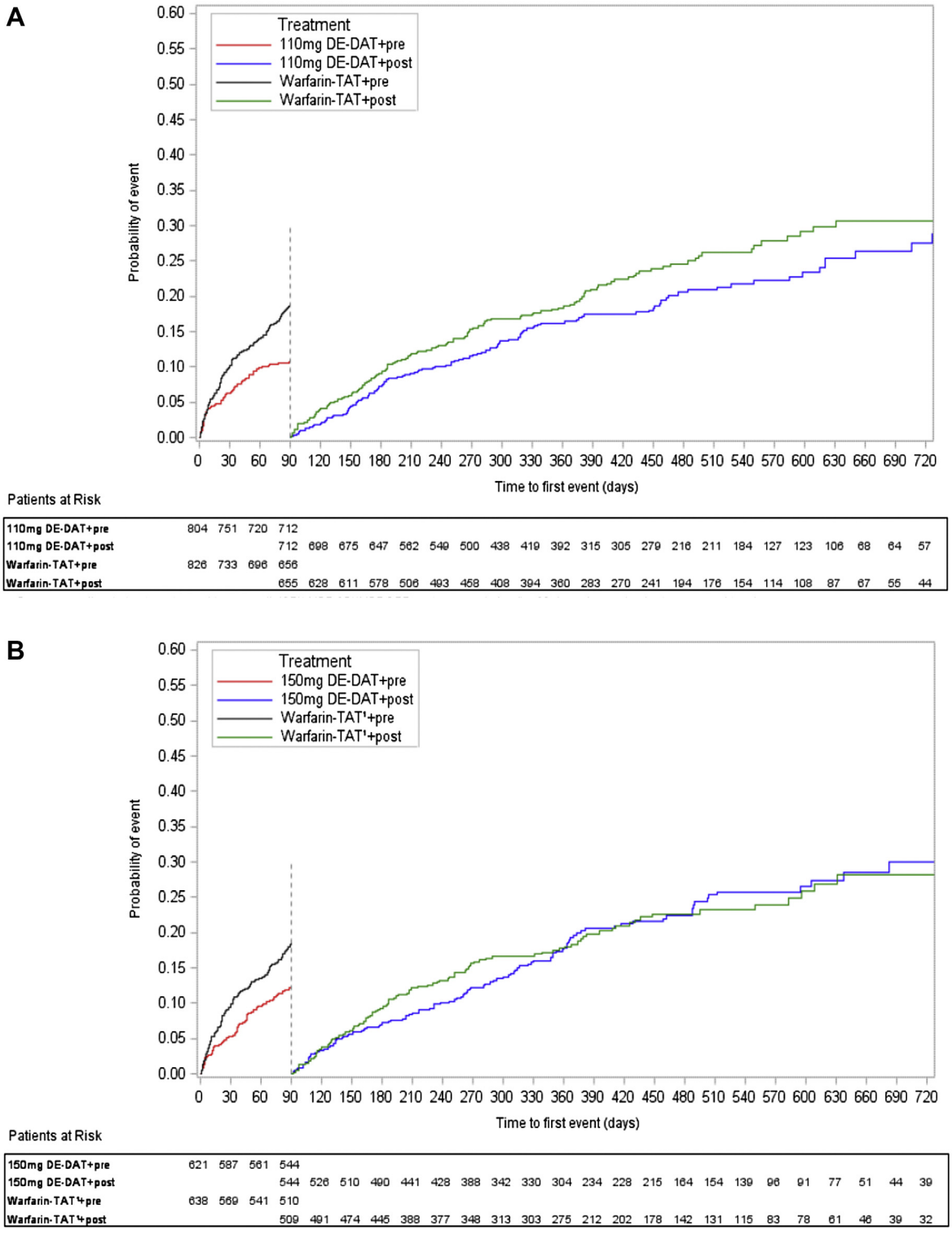
Events among patients who received drug-eluting stents during first 90 days after randomization and starting 90 days after randomization. The primary bleeding endpoint is a composite of all International Society on Thrombosis and Hemostasis (ISTH) major bleeding events (MBE) or clinically relevant nonmajor bleeding events (CRNMBE). *Cox proportional hazards model. For the dabigatran 110 mg versus warfarin comparison, the model was stratified by age, nonelderly versus elderly (<70 or ≥70 years in Japan and <80 or ≥80 years elsewhere). For the dabigatran 150 mg versus warfarin comparison, an unstratified model was used. †Wald confidence limits. ‡Wald 2-sided p value from (stratified) Cox proportional hazards model. For the comparison with dabigatran 150 mg dual therapy, elderly patients outside the United States are excluded. CI = confidence interval; HR = hazard ratio.

0.55 to 1.70; p = 0.92; stent thrombosis: 6 [1.0%] vs. 4 [0.6%]; HR: 1.52; 95% CI: 0.43 to 5.38; p = 0.52). There were numerically higher rates of DTE with dabigatran 110 mg, but not 150 mg, versus warfarin (Supplemental Table 4). During the first 90 days, there was net clinical benefit among patients treated with dabigatran 110 mg dual therapy (10.7% vs. 18.5%; HR: 0.55; 95% CI: 0.42 to 0.72; p < 0.0001) and dabigatran 150 mg dual therapy (12.2% vs. 18.2%; HR: 0.64; 95% CI: 0.48 to 0.86; p = 0.0025) versus warfarin triple therapy.

After 90 days, there was a persistent reduction in ISTH major bleeding or CRNM bleeding in patients who received dabigatran 110 mg dual therapy versus warfarin dual therapy (9.8% vs. 13.9%; HR: 0.69; 95% CI: 0.50 to 0.93; p = 0.0167). However, there was a similar bleeding risk among patients who received dabigatran 150 mg dual therapy versus warfarin dual therapy (13.7% vs. 13.1%; HR: 1.01; 95% CI: 0.73 to 1.41; p = 0.94) (Figures 2 and 3). After 90 days, there were similar rates of the secondary thrombotic endpoints among the 3 groups, with net clinical benefit with dabigatran 110 mg dual therapy versus warfarin dual therapy and similar net clinical benefit to dabigatran 150 mg dual therapy versus warfarin dual therapy (Supplemental Table 4, Supplemental Figure 2).

EXPLORATORY ANALYSES: BMS. Among patients who received BMS, there were similar reductions in bleeding in the 2 dabigatran groups versus warfarin prior to 30 days, as had been seen in the DES patients prior to 90 days. After 30 days, there was a reduction in ISTH major bleeding or CRNM bleeding with dabigatran 110 mg versus warfarin and similar rates of bleeding with dabigatran 150 mg versus warfarin (see Supplemental Figure 3). There were insufficient thrombotic events to make any comment about any of

FIGURE 3 Landmark Analysis of Patients Who Received Drug-Eluting Stents With Respect to the Primary Endpoint of ISTH Major Bleeding or CRNM Bleeding



(A) Events before and after the first 90 days after randomization in patients who received 110 dabigatran dual therapy versus warfarin triple therapy. **(B)** Events before and after the first 90 days after randomization in patients who received 150 dabigatran dual therapy versus warfarin triple therapy. CRNM = clinically relevant nonmajor bleeding; ISTH = International Society on Thrombosis and Hemostasis; other abbreviations as in Figure 1.

the secondary efficacy endpoints among patients who received a BMS.

DISCUSSION

Our study showed that in the early phase of treatment, both doses of dabigatran plus a $P2Y_{12}$ inhibitor resulted in a substantial reduction in bleeding risk compared with warfarin triple therapy. During the first 30 days, there was a 55% reduction in bleeding with dabigatran 110 mg dual therapy versus warfarin triple therapy and a 54% reduction in bleeding with dabigatran 150 mg dual therapy versus warfarin triple therapy. There were also significant reductions in recurrent bleeding events: 39% in dabigatran 110 mg dual therapy and 23% in dabigatran 150 mg dual therapy versus warfarin triple therapy.

After the removal of aspirin, dabigatran 110 mg dual therapy continued to be associated with 31% lower bleeding than warfarin dual therapy, while dabigatran 150 mg dual therapy had a similar risk for bleeding as warfarin dual therapy.

This analysis suggests that the differential risk for bleeding between warfarin triple therapy and dabigatran dual therapy seen in RE-DUAL PCI was related to both the lack of aspirin and, for the 110 mg dose, the lower level of anticoagulation; the large early reductions in bleeding seem to be driven largely by lack of aspirin in the dual-therapy arms (33–35). The post-90-day landmark data suggest that there is an additional benefit to dabigatran 110 mg versus warfarin with respect to bleeding, similar to the results of the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) study (36,37). This lower risk for bleeding when stopping aspirin has now been well established in the AUGUSTUS trial with 2 × 2 factorial randomization (12). In AUGUSTUS, however, there was an early increased risk for thrombotic events in patients who were not treated with aspirin. In this analysis, patients treated with dabigatran 150 mg dual therapy had similar and large early reductions in bleeding without an increase in thrombotic events.

FIRST 30 DAYS. During the first 30 days, neither of the 2 dual-therapy groups had significantly higher rates of DTE or unplanned revascularization. However, with great focus on these events, one could see a numerically higher rate of DTE or unplanned revascularization with dabigatran 110 mg versus warfarin (2.9% vs. 2.0%; HR: 1.39; $p = 0.26$), but not with dabigatran 150 mg dual therapy versus warfarin triple therapy (1.6% vs. 2.2%; HR: 0.70; $p = 0.34$). The number of stent thromboses and myocardial infarctions in DES patients tended to be greater during the first 90 days, but the number of events was so small that it is difficult to draw any definitive inferences.

Although a consistent benefit of the dual-therapy approaches has been seen across the 5 trials (including WOEST), the duration of aspirin post-PCI and prior to randomization to dual therapy varied across the different trials. In AUGUSTUS, the average time to randomization (and the average duration of aspirin therapy post-PCI in the patients who then were randomized to dual therapy) was 6.6 days. On the basis of these data, some clinicians have suggested that patients be treated with aspirin for 1 week following PCI (35). However, in RE-DUAL PCI, the average time from PCI to randomization was only 1.6 days; thus, the effects of a dual-therapy approach, without increased risk for thrombotic events, can apply even with just 1 or 2 days of aspirin post-PCI.

From this analysis, it seems that the increased bleeding risk of triple therapy is most pronounced early, especially during the first 30 and 90 days. Although recent practice may be to use a brief period of triple therapy during the first months after PCI, this may in fact be the time period with the highest risk for bleeding with respect to the use of triple therapy, except in select individualized cases. Given the lack of a numeric increase in thrombotic events in the early period for the dabigatran 150 mg dual-therapy regimen, with significant net benefit, this may be an appealing strategy for the early period post-PCI. As discussed in recent European and U.S. consensus statements, any use of aspirin beyond hospital discharge should be individualized and limited to those with the highest thrombotic risk and lowest bleeding risk (38–40).

The first 30 days post-PCI are the most critical, not only for the risk for thrombotic events but also bleeding. It is interesting to note that the bleeding curves and net clinical benefit curves begin to separate at about 5 days after randomization with dabigatran 150 mg dual therapy versus warfarin triple therapy, corresponding perhaps with the residual hemorrhagic effects of aspirin. Thus, in the first 30 days, removal of aspirin and treatment with dabigatran 150 mg plus a $P2Y_{12}$ inhibitor is safer and at least as effective as warfarin triple therapy, with net clinical benefit. In contrast, in a recent landmark analysis of AUGUSTUS, there were more severe thrombotic events during the first 30 days among patients treated with oral anticoagulation plus a $P2Y_{12}$ inhibitor without aspirin (22). This is a plausible benefit of the 150-mg dose, as dabigatran 150 mg previously has been shown to be more effective than warfarin at preventing ischemic stroke in RE-LY and

is the only DOAC regimen shown to have that benefit over warfarin (37,41,42). As such, this 150-mg dosing regimen of dabigatran may be ideal for many patients, especially those challenging patients with both elevated bleeding and thrombotic risk.

AFTER 30 DAYS. After 30 days, however, there was net clinical benefit with dabigatran 110 mg dual therapy versus warfarin and similar outcomes for both bleeding and thrombotic events (and the net clinical benefit endpoint) for dabigatran 150 mg dual therapy versus warfarin. As a result of this landmark analysis data, for a patient at high bleeding risk, one might consider using dabigatran 150 mg dual therapy for the first 30 days after PCI and then continuing with that dose or reducing the dose to 110 mg (if available), as a way to optimize bleeding and thrombotic risk.

Although the increase of bleeding associated with adding aspirin to warfarin has long been established, aspirin use has repeatedly been shown to increase the risk for bleeding when added to DOACs as well (10,12,18). After the discontinuation of aspirin, the reduced bleeding profile of the dabigatran 110 mg group over the warfarin group, as well as the similar bleeding profile of the dabigatran 150 group and warfarin, again parallels the results of the RE-LY trial, in which dabigatran 110 mg twice daily showed a superior bleeding profile over warfarin, while dabigatran 150 mg twice daily showed no difference in bleeding compared with warfarin (37). Unlike the other DOACs, however, dabigatran does not have specific dose reduction criteria in the United States, and a 110-mg twice-daily dose is not yet approved in the United States for atrial fibrillation, though it is approved for venous thromboembolism (in Europe, the 110-mg dose has been approved for atrial fibrillation as well) (41–43).

90-DAY LANDMARK. The 90-day landmark analysis, limited to patients who received DES, provides some important insight into the large early reductions in bleeding in both arms of dabigatran dual therapy versus warfarin because patients in the warfarin arms who received DES discontinued aspirin after 90 days. Thus, in the case of dabigatran 150 mg, the early net clinical benefit and large bleeding reduction seems to be related to the lack of aspirin alone. In contrast, in the case of dabigatran 110 mg, net clinical benefit and reductions in bleeding persist beyond 90 days, suggesting an additional benefit to lower dose anticoagulation, beyond the omission of early aspirin therapy.

STUDY LIMITATIONS. Limitations of this study include multiple comparisons that exist with any secondary analysis of a clinical trial. The RE-DUAL PCI study was not powered for this landmark analysis, nor was this a pre-specified analysis. Thus, all p values should be regarded as exploratory. Landmark analyses have inherent limitations, including the introduction of survival bias, the arbitrariness of a landmark cutoff, and the erosion of randomization for the post-cutoff period. The higher pre-landmark risk for bleeding in the warfarin groups likely skews the post-landmark results in favor of the warfarin therapy group, because surviving patients who were free from the primary bleeding endpoint at the landmark cutoff were included, leading to the selection of those who did not bleed. We did not investigate relative bleeding rates among patients who were treated with clopidogrel versus ticagrelor, but in a recent analysis, Oldgren et al. (44) showed that there was a consistent benefit with dabigatran dual versus warfarin triple therapy in patients who were treated with clopidogrel or with ticagrelor in RE-DUAL PCI. Other limitations of this study are shared with the RE-DUAL PCI study, such as the lack of a comparison arm with warfarin and no aspirin (24). The effect of aspirin in combination with dabigatran was not studied in RE-DUAL PCI; only the AUGUSTUS trial was able to compare warfarin versus DOAC dual therapy prospectively. In addition, RE-DUAL PCI was not powered to detect differences in thrombotic events; the same is true for each of the trials studying DOACs in patients with atrial fibrillation who undergo PCI (45). Yet it is encouraging that the number of thrombotic events is this small, even if any inferences we may draw from between-group comparisons are limited.

CONCLUSIONS

Both doses of dabigatran plus a $P2Y_{12}$ inhibitor markedly reduced the risk for early bleeding compared with warfarin triple therapy. There was early net clinical benefit with both doses of dabigatran dual therapy versus warfarin triple therapy, without a numeric increase in thrombotic events in patients treated with dabigatran 150 mg dual therapy. After 30 days and after aspirin was discontinued, 110 mg dabigatran dual therapy continued to have a lower bleeding risk than warfarin dual therapy, and 150 mg dabigatran dual therapy had a similar bleeding risk profile to warfarin dual therapy. On the basis of this exploratory analysis, either combination could be

a safe substitution for warfarin when combined with a $P2Y_{12}$ inhibitor, without the need for aspirin at any point after the doses received peri-PCI, except in select cases (40). At the same time, our analysis suggests the benefits observed can be achieved with a briefer period of aspirin therapy immediately post-PCI (1 to 2 days) than was used in AUGUSTUS (6 to 7 days). In addition, given the net clinical benefit, dabigatran 150 mg may be considered to allow reduced bleeding and no numeric increase in thrombotic events, especially among the subset of patients who have elevated risk for both bleeding and thrombotic events.

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PERSPECTIVES

WHAT IS KNOWN? Patients with atrial fibrillation who undergo PCI are at significantly increased risk for both bleeding and thrombotic events.

WHAT IS NEW? In a landmark analysis of the RE-DUAL PCI trial, there were large reductions in the primary bleeding endpoint before 30 days, without a significant increase in thrombotic events in patients treated with dabigatran dual therapy versus warfarin triple therapy.

WHAT IS NEXT? Further investigation of the tolerability and efficacy of dual-antithrombotic therapy among patients at particularly increased risk for ischemic events or with recurrent ischemic events is warranted.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.